

**EXHIBIT B**

**MARKED-UP VERSION OF THE CLAIMS  
U.S. PATENT APPLICATION NO. 09/518,081**

1. (Twice Amended) A method of inhibiting apoptosis in a subject, comprising:  
  
administering a therapeutically effective amount of at least one serine protease inhibitor in which  
the effective amount inhibits apoptosis;

wherein the subject suffers from at least one of wasting disease, neurodegenerative  
disease, myocardial infarction, stroke, Alzheimer's disease, arthritis, muscular dystrophy, Downs  
Syndrome, sepsis, HIV infection, multiple sclerosis, arteriosclerosis, diabetes[, arthritis],  
autoimmune disease, ischemia-reperfusion injury, or toxin-induced liver injury.

3. (Amended) The method of Claim 1, in which the serine protease inhibitor is  
 $\alpha_1$ -antitrypsin, [an  $\alpha_1$ -antitrypsin-like agent, a variant of  $\alpha_1$ -antitrypsin, an antikathepsin G  
agent, an antitryptase TL-2 agent, an antifactor Xa agent, an antielastase agent, an antiproteinase-  
3 agent,]an oxidation-resistant or free radical-resistant variant thereof, or combinations thereof.

4. (Twice Amended) The method of Claim 3 in which the effective amount is [greater  
than 0.2]at least .001 and [less than 8.0]no greater than 70 g/kg body weight.

8. (Twice Amended) The method of Claim 1, in which the serine protease inhibitor is  
selected from the group consisting of:

- i. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- ii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- iii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- iv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- v. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(methyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- vi. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(difluoromethyl)-1,2,4-oxadiazolyl)[ ]carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- vii. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(benzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- viii. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(3-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- ix. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(2,6-difluorobenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- x. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(trans-styryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- xi. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(trans-4-[T]trifluoromethylstyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

- xii. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(trans-4-[M]methoxystyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- xiii. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(3-[T]thienylmethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- xiv. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-([P]phenyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xv. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(3-[P]phenylpropyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- xvi. [B](benzyloxycarbonyl)-L-valyl-N-[1-(2-([ ])(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]-L-prolinamide (also known as CE-2072)[,];
- xvii. [B](benzyloxycarbonyl)-L-valyl-N-[1-(2-(3-(methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xviii. [B](benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(methyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-[ ]2-(S)-methylpropyl]-L-prolinamide;
- xix. [B](benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-trifluoromethylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xx. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(4-[D]dimethylamino[ ]benzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxi. [B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(1-naphthyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxii. ([B]benzyloxycarbonyl)-L-valyl-[1-(3-(5-(3,4-methylenedioxybenzyl)-1,2,4[ ]-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

- xxiii. [B](benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethylbenzyl)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxiv. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethoxybenzyl)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxv. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-ditrifluoromethylbenzyl)-1,2,4-[ ]-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxvi. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxvii. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(biphenylmethine)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxviii. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-phenylbenzyl)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxix. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylbenzyl)-1,2,4-[ ]-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxx. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenoxybenzyl)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxxi. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(cyclohexylmethylene)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxxii. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethyldimethylmethylene[ ]) -1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxxiii. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(1-naphthylmethylene)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

- xxxiv. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-pyridylmethyl)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxxv. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-diphenylbenzyl)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxxvi. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-dimethylaminobenzyl)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxxvii. 2-[(][5-[(B]benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ])]carbonyl)-[ ](S)-2-methylpropyl]acetamide;
- xxxviii. 2-(5-[A]amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl)-N-[1-(3-(5-[ ](3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- xxxix. 2-[(][5-[(B]benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-(S)-2-methylpropyl]acetamide;
- xl. 2-[(][5-[A]amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-[ ](3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-methylpropyl]acetamide;
- xli. ([P]pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]amide;
- xlii. ([P]pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)[ ](-1,2,4-oxadiazolyl)-(S)-methylpropyl]amide;

- xl. (2S,5S)-5-[A]amino-1,2,4,5,6,7-hexahydroazepino-[3,2,1]-indole-4-one-carbonyl[ ]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-(R,S)-2-methylpropyl]amide;
- xli. BTD-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]amide;
- xlii. (R,S)-3-[A]amino-2-oxo-5-phenyl-1,4[,]benzodiazepine-N-[1-(2-(5-(3-methylbenzyl[ ])-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- xliii. ([B]benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]amide;
- xliiii. ([B]benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]amide;
- xlv. [A]acetyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]amide;
- xlvi. 3-(S)-([B]benzyloxycarbonyl)amino)-ε-lactam-N-[1-(2-(5-(3-methylbenzyl[ ])-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- xlvii. 3-(S)-([A]amino)-ε-[ ]lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide trifluoroacetic acid salt;
- xlviii. 3-(S)-[(4-morpholino[ ]carbonyl-butanoyl)amino]-ε-[ ]lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(R,S)-methylpropyl]acetamide;
- xlix. 6-[4-[F]fluorophenyl]-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- l. 2-(2-(R,S)-[P]phenyl-4-oxothiazolidin-3-yl)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;

- liv. 2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4[ ]-oxadiazolyl[ ])]hydroxymethyl)-2-(S)-methylpropyl]acetamide;
- lv. 2-(2-(R,S)-[B]benzyl-4-oxothiazolidin-3-yl)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4[ ]-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl][ ]acetamide;
- lvi. 2-(2-(R,S)-[B]benzyl-4-oxothiazolidin-3-yl oxide)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-[ ](R,S,-methylpropyl]acetamide;
- lvii. (1-[B]benzoyl-3,8-quinazolinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lviii. (1-[B]benzoyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lix. (1-[P]phenyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lx. [ ](1-[P]phenyl-3,6-piperazinedione)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4[ ]-oxadiazolyl[ ])]carbonyl)]-2-(S)-methylpropyl]acetamide;
- lxi. 3-([(B]benzyloxycarbonyl)amino]-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lxii. 3-([(B]benzyloxycarbonyl)amino]-7-piperidinyl-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lxiii. 3-([C]carbomethoxy-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lxiv. 3-([A]amino-quinolin-2-one)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;

- lxv. 3-[(4-[M]morpholino)aceto]amino-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxvi. 3,4-[D]dihydro-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxvii. 1-[A]acetyl-3-(4-fluorobenzylidene[ ]piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxviii. 1-[A]acetyl-3-(4-dimethylamino[ ]benzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxix. 1-[A]acetyl-3-(4-carbomethoxy[ ]benzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxx. 1-[A]acetyl-3-[(4-pyridyl)methylene]piperazine-2,5-dione-N-[1-(2-(5-(3-methyl[ ]benzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxi. 4-[1-[B]benzyl-3-(R)-benzyl-piperazine-2,5[,]-dione]-N-[1-(2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxii. 4-[1-[B]benzyl-3-(S)-benzyl[ ]piperazine-2,5[,]-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxiii. 4-[1-[B]benzyl-3(R)-benzylpiperazine-2,5[,]-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxiv. 4-[1-[B]benzyl-3-(S)-benzylpiperazine-2,5[,]-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxv. 4-[1-[B]benzyl-3-(S)-benzyl[ ]piperazine-2,5[,]-dione]-N-[1-(3-(5-(2-dimethylaminoethyl)-1,2,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;



- lxxvi. 4-[1-[M]methyl-3-(R,S)-phenylpiperazine-2,5[,]-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[[]])carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxvii. 4-[[][-M]methyl-3-(R,S)-phenyl[ ]piperazine-2,5[,]-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[[]])carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxviii. 4-[1-(4-[M]morpholino[ ]ethyl)3-(R)-benzyl[ ]piperazine-2,5[,]-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[[]])carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxix. 5-(R,S)-[P]phenyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[[]])carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxx. 5-(R)-[B]benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[[]])carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxxi. 5-(S)-[B]benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[[]])carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxxii. 5-(S)-[B]benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1[,2,4-oxadiazolyl[[]])carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxxiii. 5-(R)-[B]benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1[,2,4-oxadiazolyl[[]])carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxxiv. 1-[B]benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1[,3,4-oxadiazolyl[[]])carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxxv. 1-[B]benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethyl[ ]benzyl)-1,2,4-oxadiazolyl[[]])carbonyl)-2-(S)-methylpropyl]acetamide[,];
- pharmaceutically acceptable salts thereof[,];
- and combinations thereof.

9. (Twice Amended) The method of Claim 8, in which the effective amount is at least 0.001 and [less than 8.0]no greater than 7.0 g/kg body weight.

12. (Twice Amended) The method of Claim 1, in which the therapeutically effective amount is sufficient to provide at least [8]10 pM and [less than 3]no greater than 2 mM of the inhibitor in the biological fluid of the subject.

14. (Twice Amended) The method of Claim 1, in which the therapeutically effective amount is sufficient to provide at least [2].5  $\mu$ M and [less than 220]no greater than 200  $\mu$ M in the biological fluid of the subject.

16. (Twice Amended) The method of Claim 1, in which the therapeutically effective amount is administered at least once daily and no more than once hourly.

18. (Amended) A method of prophylactically treating an individual at risk for a pathological condition that is precipitated at least in part by excessive apoptosis, comprising:  
administering to an individual a therapeutically effective amount of at least one [agent exhibiting mammalian  $\alpha_1$ -antitrypsin or  $\alpha_1$ -antitrypsin-like activity]serine protease inhibitor.

19. (Amended) A method for [inhibiting]reducing apoptosis in an in vitro mammalian cell culture, an *ex vivo* mammalian tissue culture, or mammalian organ comprising:

providing to a cell culture, tissue culture, or organ an amount of a serine protease inhibitor sufficient to inhibit apoptosis in said cell culture, tissue culture, or organ wherein a measured amount of apoptosis is indicative of apoptosis activity.

23. (Twice Amended) The method of Claim [21]25, in which the serine protease inhibitor is derivatized by esterification, acetylation, or amidation, and wherein the derivatized serine protease inhibitor retains the inhibitory activity.

24. (Twice Amended) The method of Claim [23]25, wherein the at least one cell is a cell of a subject, and wherein the amount is sufficient to bring the concentration of serine protease inhibitor in the subject's blood to at least [2].5  $\mu\text{M}$  and [less than 220]no greater than 200  $\mu\text{M}$ .

25. (Twice Amended) A method of reducing apoptosis, comprising providing a serine protease inhibitor to at least one cell and measuring a decrease in apoptosis, wherein the serine protease inhibitor is an oxidation-resistant or free radical-resistant variant of  $\alpha_1$ -antitrypsin; or:

- i. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- ii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-phenylethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

- iii. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(2-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- iv. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(trifluoromethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- v. (benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(methyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- vi. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(difluoromethyl)-1,2,4-oxadiazolyl)[ ]carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- vii. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(benzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- viii. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(3-methoxybenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- ix. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(2,6-difluorobenzyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- x. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(trans-styryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- xi. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(trans-4-[T]trifluoromethylstyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- xii. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(trans-4-[M]methoxystyryl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- xiii. ([B]benzyloxycarbonyl)-L-[V]valyl-N-[1-(3-(5-(3-[T]thienylmethyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;

- xiv. ([B]benzyloxycarbonyl)-L-[V]yalyl-N-[1-(3-(5-([P]phenyl)-1,2,4-oxadiazolyl)carbonyl[ ])-2-(S)-methylpropyl]-L-prolinamide;
- xv. ([B]benzyloxycarbonyl)-L-[V]yalyl-N-[1-(3-(5-(3-[P]phenylpropyl)-1,2,4-oxadiazolyl)carbonyl)-2-(S)-[M]methylpropyl]-L-[P]prolinamide;
- xvi. [B](benzyloxycarbonyl)-L-valyl-N-[1-(2-[[ ](5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]])carbonyl)-2-(S)-methylpropyl]-L-prolinamide (also known as CE-2072)[,];
- xvii. [B](benzyloxycarbonyl)-L-valyl-N-[1-(2-(3-(methylbenzyl)-1,3,4-oxadiazolyl[ ]])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xviii. [B](benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(methyl)-1,3,4-oxadiazolyl[ ]])carbonyl)-[ ]2-(S)-methylpropyl]-L-prolinamide;
- xix. [B](benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(3-trifluoromethylbenzyl)-1,3,4-oxadiazolyl[ ]])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xx. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(4-[D]dimethylamino[ ]benzyl)-1,3,4-oxadiazolyl[ ]])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxi. [B]benzyloxycarbonyl)-L-valyl-N-[1-(2-(5-(1-naphthylenyl)-1,3,4-oxadiazolyl[ ]])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxii. ([B]benzyloxycarbonyl)-L-valyl-[1-(3-(5-(3,4-methylenedioxybenzyl)-1,2,4[ ]-oxadiazolyl[ ]])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxiii. [B](benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethylbenzyl)-1,2,4-oxadiazolyl[ ]])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxiv. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-dimethoxybenzyl)-1,2,4-oxadiazolyl[ ]])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

- xxv. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-ditrifluoromethylbenzyl)-1,2,4-oxadiazolyl[  ])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxvi. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-methylbenzyl)-1,2,4-oxadiazolyl[  ])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxvii. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(biphenylmethine)-1,2,4-oxadiazolyl[  ])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxviii. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-phenylbenzyl)-1,2,4-oxadiazolyl[  ])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxix. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenylbenzyl)-1,2,4-oxadiazolyl[  ])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxx. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-phenoxybenzyl)-1,2,4-oxadiazolyl[  ])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxxi. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(cyclohexylmethylene)-1,2,4-oxadiazolyl[  ])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxxii. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-trifluoromethyldimethylmethylene[  ])-1,2,4-oxadiazolyl[  ])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxxiii. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(1-naphthylmethylene)-1,2,4-oxadiazolyl[  ])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxxiv. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3-pyridylmethyl)-1,2,4-oxadiazolyl[  ])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;
- xxxv. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(3,5-diphenylbenzyl)-1,2,4-oxadiazolyl[  ])carbonyl)-2-(S)-methylpropyl]-L-prolinamide;

xxxvi. ([B]benzyloxycarbonyl)-L-valyl-N-[1-(3-(5-(4-dimethylaminobenzyl)-1,2,4-oxadiazolyl[ ]))carbonyl]-2-(S)-methylpropyl]-L-prolinamide;

xxxvii. 2-([(5-[(B]benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ]))carbonyl]- ](S)-2-methylpropyl]acetamide;

xxxviii. 2-(5-[A]amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(3-(5-[ ](3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ]))carbonyl]-2-(S)-methylpropyl]acetamide;

xxxix. 2-([(5-[(B]benzyloxycarbonyl)amino]-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl]- (S)-2-methylpropyl]acetamide;

xl. 2-([(5-[A]amino-6-oxo-2-(4-fluorophenyl)-1,6-dihydro-1-pyrimidinyl]-N-[1-(2-(5-[ ](3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl]-2-methylpropyl]acetamide;

xli. ([P]pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl]-2-(S)-methylpropyl]amide;

xl.ii. ([P]pyrrole-2-carbonyl)-N-(benzyl)glycyl-N-[1-(3-(5-(3-trifluoromethylbenzyl)[ ](-1,2,4-oxadiazolyl)-(S)-methylpropyl]amide;

xl.iii. (2S,5S)-5-[A]amino-1,2,4,5,6,7-hexahydroazepino-[3,2,1]-indole-4-one-carbonyl[ ]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl]- (R,S)-2-methylpropyl]amide;

xl. iv. BTD-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl]-2-(S)-methylpropyl]amide;

- xliv. (R,S)-3-[A]amino-2-oxo-5-phenyl-1,4[,]benzodiazepine-N-[1-(2-(5-(3-methylbenzy[ ]l)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- xlvi. ([B]benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]amide;
- xlvii. ([B]benzyloxycarbonyl)-L-valyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]amide;
- xlvi. [A]acetyl-2-L-(2,3-dihydro-1H-indole)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]amide;
- xlix. 3-(S)-([B]benzyloxycarbonyl)amino)-ε-lactam-N-[1-(2-(5-(3-methylbenzy[ ]l)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- i. 3-(S)-([A]amino)-ε-[ ]lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide trifluoroacetic acid salt;
- li. 3-(S)-[(4-morpholino[ ]carbonyl-butanoyl)amino]-ε-[ ]lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3[, ]4-oxadiazolyl[ ]))carbonyl)-2-(R,S)-methylpropyl]acetamide;
- lii. 6-[4-[F]fluorophenyl]-ε-lactam-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- liii. 2-(2-(R,S)-[P]phenyl-4-oxothiazolidin-3-yl)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4[ ]-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- liv. 2-(2-(R,S)-phenyl-4-oxothiazolidin-3-yl)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4[ ]-oxadiazolyl[ ]))hydroxymethyl)-2-(S)-methylpropyl]acetamide;
- lv. 2-(2-(R,S)-[B]benzyl-4-oxothiazolidin-3-yl)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4[ ]-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl][ ]acetamide;



- lvi. 2-(2-(R,S)-[B]benzyl-4-oxothiazolidin-3-yl oxide)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ]))carbonyl)-2-[ ](R,S)-methylpropyl]acetamide;
- lvii. (1-[B]benzoyl-3,8-quinazolinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lviii. (1-[B]benzoyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lix. (1-[P]phenyl-3,6-piperazinedione)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lx. [ ](1-[P]phenyl-3,6-piperazinedione)-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-[ ]-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxi. 3-([(B]benzyloxycarbonyl)amino]-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxii. 3-([(B]benzyloxycarbonyl)amino]-7-piperidinyl-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxiii. 3-([C]carbomethoxy-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxiv. 3-([A]amino-quinolin-2-one)-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxv. 3-[(4-[M]morpholino)aceto]amino-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxvi. 3,4-[D]dihydro-quinolin-2-one-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;

- lxvii. 1-[A]acetyl-3-(4-fluorobenzylidene)[ ]piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxviii. 1-[A]acetyl-3-(4-dimethylamino[ ]benzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxix. 1-[A]acetyl-3-(4-carbomethoxy[ ]benzylidene)piperazine-2,5-dione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxx. 1-[A]acetyl-3-[(4-pyridyl)methylene]piperazine-2,5-dione-N-[1-(2-(5-(3-methyl[ ]benzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxi. 4-[1-[B]benzyl-3-(R)-benzyl-piperazine-2,5[,]-dione]-N-[1-(2-[5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxii. 4-[1-[B]benzyl-3-(S)-benzyl[ ]piperazine-2,5[,]-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxiii. 4-[1-[B]benzyl-3(R)-benzylpiperazine-2,5[,]-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxiv. 4-[1-[B]benzyl-3-(S)-benzylpiperazine-2,5[,]-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxv. 4-[1-[B]benzyl-3-(S)-benzyl[ ]piperazine-2,5[,]-dione]-N-[1-(3-(5-(2-dimethylaminoethyl)-1,2,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxvi. 4-[1-[M]methyl-3-(R,S)-phenylpiperazine-2,5[,]-dione]-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1,2,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxvii. 4-[1-[M]methyl-3-(R,S)-phenyl[ ]piperazine-2,5[,]-dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ]))carbonyl)-2-(S)-methylpropyl]acetamide;

- lxxviii. 4-[1-(4-[M]morpholino[ ]ethyl)3-(R)-benzyl[ ]piperazine-2,5[,]dione]-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxix. 5-(R,S)-[P]phenyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxx. 5-(R)-[B]benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxxi. 5-(S)-[B]benzyl-2,4-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxxii. 5-(S)-[B]benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1[,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxxiii. 5-(R)-[B]benzyl-2,4-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethylbenzyl)-1[,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxxiv. 1-[B]benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(2-(5-(3-methylbenzyl)-1[,3,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide;
- lxxxv. 1-[B]benzyl-4-(R)-benzyl-2,5-imidazolidinedione-N-[1-(3-(5-(3-trifluoromethyl[ ]benzyl)-1,2,4-oxadiazolyl[ ])]carbonyl)-2-(S)-methylpropyl]acetamide[,];
- pharmaceutically acceptable salts thereof[,];
- and combinations thereof.